REMARKS

I. Status of the Claims

Claims 1-40 were originally filed and later canceled. Claims 41-48 were added and are currently pending.

II. Objection to the Specification

The Examiner objected to the specification for containing an embedded hyperlink. The present amendment to the specification has deleted this hyperlink.

III. Claim Rejections

A. 35 U.S.C. §112 First Paragraph Enablement Requirement

Claims 41-48 were rejected under 35 U.S.C. §112 first paragraph for alleged failure to meet the enablement requirement. The Examiner stated that while enabling for nucleic acids of SEQ ID NOs:1, 2, and 3, and that encode polypeptides of SEQ ID NOs:4 and 5, the specification does not adequately enable one of skill in the art to make and use the entire genus of claimed nucleic acids (the bridging paragraph between pages 3 and 4). Specifically, the Examiner found the claimed invention inadequately enabled because " the specification does not teach all possible nucleic acid variants that hybridize to a nucleic acid encoding an amino acid sequence of SEQ ID NO:4 or 5" (the bridging paragraph between pages 4 and 5). The Examiner further cited unpredictability of protein function upon amino acid substitutions as a reason for finding inadequate enablement (the bridging paragraph between pages 5 and 6 and the first full paragraph on page 6).

Applicant respectfully traverses the rejection. A claimed invention is enabled when the disclosure allows one of ordinary skill in the art to make and use the invention without undue experimentation. MPEP §2164.01. The test for enablement as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), requires the consideration of multiple factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of predictability in the art; the amount of direction provided by the

inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the present case, the claims are directed to nucleic acids encoding a subunit of a KCNQ potassium channel with a well-defined structure and readily testable functional features. Working examples of human KCNQ coding sequence and amino acid sequence are provided (*see, e.g.*, SEQ ID NOs:2-5). The specification also contains ample directions to practice the invention, such as methods of cloning KCNQ nucleic acid sequences (*see, e.g.*, page 26 line 27 to page 29 line 4), expression of KCNQ nucleic acid sequences (*see, e.g.*, page 29 line 7 to page 31 line 14), purifications of KCNQ polypeptides (*see, e.g.*, page 31 line 16 to page 34 line 11), immunological detection of KCNQ polypeptides (*see, e.g.*, page 34 line 14 to page 41 line 17), and assays for modulators of KCNQ (*see, e.g.*, page 41 line 20 to page 48 line 14). The level of technical sophistication is high in the art, and the KCNQ potassium channel variants can be readily tested according to the methods commonly used by those skilled in the art or the methods taught by the specification (such as nucleic acid or amino acid sequence comparison, nucleic acid hybridization assays, and assays for ion channels with the characteristics of voltage-gating) to eliminate inoperable embodiments. MPEP §2164.01 states, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. In the present case, although some experimentation may be involved to practice the claimed invention using embodiments other than those specifically described in the application, such experimentation utilizes well-established techniques and is the type routinely conducted in the art. Thus, the experimentation does not constitute undue experimentation. Taken together, analysis of the *Wands* factors indicates proper enablement of the claimed invention.

In response to the Examiner's specific concern that "the specification does not teach all possible nucleic acid variants that hybridize to a nucleic acid encoding an amino acid sequence of SEQ ID NO:4 or 5," Applicant respectfully notes that one need not disclose all possible embodiments to meet the enablement requirement. According to

MPEP §2164.03, "even in unpredictable art, a disclosure of every operable species is not required [for enablement]."

The Examiner appeared to believe that the conclusion of inadequate enablement is supported by the unreliable nature of predicting protein functionality based on amino acid sequence homology and stated, "one skilled in the art would not be able to predict that the claimed nucleic acid degenerates would encode a protein having biological activities similar to known KCNQ variants of SEQ ID NOs:4 and 5." Applicant agrees with the Examiner in that amino acid sequence homology alone may fail to provide a reasonable indication of a protein's function. For this precise reason, the claimed nucleic acids are defined, in addition to a sequence-based structural feature, by a functional feature: the ability to form a voltage-gated KCNQ potassium channel with at least one other KCNQ alpha subunit. This functional feature is readily testable by an ordinarily skilled artisan according to the methods known in the art or taught by the instant disclosure (*see, e.g.*, page 41 line 20 to page 48 line 14). Inoperable embodiments are thus effectively eliminated from the claimed invention. Applicant contends that such testing is the kind routinely carried out by those skilled in the art and, according to MPEP § 2164.01, cannot be considered "undue experimentation."

In summary, Applicant believes that the present disclosure is sufficiently enabling for a person with ordinary skill in the art to practice the claimed invention and that no undue experimentation is required. The rejection for inadequate enablement is improper and should thus be withdrawn.

B. 35 U.S.C. §112 First Paragraph Written Description Requirement

The Examiner also rejected claims 41-48 under 35 U.S.C. §112 first paragraph for alleged failure to meet the written description requirement. Specifically, the Examiner stated that "the specification does not teach functional or structural characteristics of the polynucleotide variants in the context of a cell or organism" and that the disclosure provides some examples of the claimed genus of nucleic acids but does not adequately describe the entire genus (the first full paragraph on page 8). The Examiner

specifically cited *Fiddes v. Baird*, 30 USPQ2d 1481 (USPTO Board of Patent Appeal and Interferences, 1993), to support the position that disclosure of a single species provides inadequate written description for a genus.

Applicant respectfully traverses the rejection. The pending claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Finally, the MPEP states that structural formulas provide a convenient method of demonstrating possession of specific molecules. MPEP §2163.

On the other hand, proper description of functional features of a claimed invention can play an important role in satisfying the written description requirement. The Federal Circuit recently stated that "*Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

With regard to the claimed nucleic acids, claim 41 (and hence its dependent claims) sets forth both functional features, *e.g.*, encoding a polypeptide comprising an alpha subunit of a KCNQ potassium channel, which polypeptide forms, with at least one additional KCNQ alpha subunit, a voltage-gated KCNQ potassium channel, and structural features, *e.g.*, capable of specifically hybridizing to a nucleic acid encoding an amino acid sequence of SEQ ID NO:5 under specified hybridization conditions.

The ability for a nucleic acid to hybridize under given conditions to a reference polynucleotide sequence, such as a DNA sequence encoding a particular amino acid sequence, is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule. *See, e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, pages 9.47-9.51 (2nd ed. 1989), attached as Exhibit A; Stryer, *Biochemistry*, pages 80-82 (3rd ed. 1988), attached as Exhibit B. As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*).

The functional features of the claimed nucleic acids are also provided: each encodes a polypeptide comprising an alpha subunit of a KCNQ potassium channel, which polypeptide forms, with at least one additional KCNQ alpha subunit, a voltage-gating KCNQ potassium channel. These functional features can be readily tested by one of ordinary skill in the art using well established, routinely practiced techniques as well as according to the teaching of the present specification.

Thus, both structural and functional features commonly shared by the claimed genus have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Such description is consistent with the standards set forth in both *Lilly* and *Amgen*.

With regard to the case cited by the Examiner, the Board ruled in *Fiddes* that adequate written description was not present to support a broad claim drawn to mammalian fibroblast growth factors (FGF) when only bovine pituitary FGF amino acid sequence and its theoretical nucleotide sequences were disclosed. The Examiner apparently was of the opinion that the facts in *Fiddes* are analogous to that in the present case, such that a finding of inadequate written description in the present application is

warranted. Applicant respectfully disagrees with the Examiner's reading of the *Fiddes* case and application of *Fiddes* in the present case.

First, *Fiddes v. Baird* is not inconsistent with the standards for written description as set forth by *Lilly* or *Fiers*. In fact, the Board in *Fiddes* quoted *Fiers* in the discussion of what constitutes adequate written description. 30 USPQ2d at 1483. Moreover, the *Lilly* decision was handed down later in time than *Fiddes* (1997 v. 1993) and by a higher legal authority (Fed. Cir. v. the Board). Thus, even if any inconsistency existed, the *Lilly* decision would tramp *Fiddes*.

Second, the fact pattern of *Fiddes* is not analogous to that of the present case. In *Fiddes*, a broad claim was drawn to mammalian FGF based on the specification disclosing a bovine FGF amino acid sequence and a ***deduced*** polynucleotide sequence, but not any naturally occurring FGF polynucleotide sequence. As it later turned out, the deduced polynucleotide sequence disclosed in the specification is significantly different from the naturally occurring FGF polynucleotide sequence, largely due to codon degeneracy. In essence, the patent applicants in *Fiddes* sought to patent a large genus of polypeptide and polynucleotides when they did not have in their possession any correct polynucleotide sequence. The Board's finding of inadequate written description was based on the notion that the claim of a genus of polynucleotides cannot be adequately supported when only an ***inaccurate*** polynucleotide sequence was disclosed. The Board in *Fiddes* did not take the position that the claim of a genus cannot be adequately supported by the disclosure of an ***accurate*** polynucleotide sequence. Nor could the Board, under *Lilly*, properly require the claim of a genus to be supported by the patent applicant's possession of every embodiment of the genus.

In contrast to *Fiddes*, Applicant of the present application has in his possession both the amino acid sequences of two KCNQ potassium channel subunits (SEQ ID NOs:2 and 3) and the naturally occurring nucleotide sequences encoding the subunits (SEQ ID NOs:4 and 5). In addition, the claims in the present application are not drawn to a broad genus of molecules without specific structural or functional definition

using *Fiddes*-type vague terms (such as mammalian KCNQ potassium channel subunits). As discussed above, both structural and functional features commonly shared by all members of the claimed genus have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

Taken together, the disclosure by the present application provides both the structural/physical features and functional characteristics of the claimed genus of KCNQ potassium channels, fully satisfying the written description requirement under *Lilly* and *Fiers*. On the other hand, there exists crucial factual distinction between the present case and *Fiddes v. Baird*, which would make it improper to apply the conclusion of *Fiddes* mechanically. As such, Applicant respectfully requests that the Examiner withdraw the written description rejection under 35 USC §112 first paragraph.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

In the bridging paragraph between pages 20 and 21:

--A preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al., Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul *et al., J. Mol. Biol.* 215:403-410 (1990), respectively. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information [(http://www.ncbi.nlm.nih.gov/)]. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al., supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide

sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.--

APPENDIX B

CLAIMS UNDER EXAMINATION

41. (as filed) An isolated nucleic acid encoding a polypeptide comprising an alpha subunit of a KCNQ potassium channel, wherein said polypeptide forms, with at least one additional KCNQ alpha subunit, a KCNQ potassium channel having the characteristic of voltage-gating; and wherein said nucleic acid specifically hybridizes under stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO:5, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS.

42. (as filed) The isolated nucleic acid of claim 41, wherein said nucleic acid selectively hybridizes under stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO:4, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS.

43. (as filed) The isolated nucleic acid of claim 41, wherein said nucleic acid encodes a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5.

44. (as filed) The isolated nucleic acid of claim 41, wherein said nucleic acid has a nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3.

45. (as filed) The nucleic acid of claim 41, wherein the polypeptide encoded by the nucleic acid comprises an alpha subunit of a homomeric potassium channel.

46. (as filed) The nucleic acid of claim 41, wherein the polypeptide encoded by the nucleic acid comprises an alpha subunit of a heteromeric potassium channel.

47. (as filed) An expression vector comprising a nucleic acid of claim 41.

48. (as filed) A host cell transfected with the vector of claim 47.